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Applicant:	Bannon, et al.	Examiner:	Huynh, P.
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For:	METHODS AND REAGENTS FOR DECREASING CLINICAL REACTIONS TO ALLERGY		

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March 23, 2004 — Date
Kathy Hart Gagnon — Signature
Kathy Hart Gagnon

Sir:

AMENDED APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Applicant appeals to the Board of Patent Appeals and Interferences (the "Board") from the Examiner's rejection of claims 37-71. A Notice to this effect was filed pursuant to 37 C.F.R. § 1.191(a) on November 7, 2002. The stamped return postcard that was filed with the Notice was received by Applicant indicating that the Notice was received by the Patent and Trademark Office on November 12, 2002. An original Appeal Brief (the "Original Brief") was filed on June 12, 2003 along with a Petition under 37 C.F.R. § 1.136 for a five (5) month extension of time, from January 12, 2003, up to and including June 12, 2003. That filing also included checks to cover the $985.00 fee under 37 C.F.R. § 1.17(a)(5) for the Petition and the $160.00 fee under 37 C.F.R. § 1.17(c) for the Appeal Brief.

A Notification of Non-Compliance with 37 C.F.R. § 1.192(c) was mailed by the Patent Office on September 23, 2003. Applicant is hereby filing an amended Appeal Brief (the "Amended Brief") that corrects the items identified in the Notification. Pursuant to 37 C.F.R. § 1.192(a), this Amended Brief is being filed in triplicate. A Petition under 37 C.F.R. § 1.136 for a five (5) month extension of time, from October 23, 2003, up to and including March 23, 2004 is also enclosed with a check to cover the $1005.00 fee under 37 C.F.R. § 1.17(a)(5). Please charge any additional fees (or credit any overpayment), to our Deposit Account 03-1721.

Real Parties in Interest

As a result of assignments by the inventors in parent application U.S. Serial No. 09/141,220 filed August 27, 1998, the real parties in interest in this application are the University of Arkansas ("UArk"), SEER Pharmaceuticals LLC (f/k/a Panacea Pharmaceuticals, LLC), and the Mt. Sinai School of Medicine of the City University of New York ("Mt Sinai"). An assignment from inventors Garry Bannon and Wesley Burks to UArk was recorded in the Patent and Trademark Office on April 23, 1999 at Reel 010065, Frame 0008. An assignment from inventor Howard Sosin to Panacea Pharmaceuticals, LLC was recorded in the Patent and Trademark Office on August 26, 1999 at Reel 010190, Frame 0516. A Certificate of Amendment changing the name of Panacea Pharmaceuticals, LLC to SEER Pharmaceuticals, LLC was filed with the Secretary of State of the State of Delaware on October 25, 2002. An assignment from inventor Hugh Sampson to Mt Sinai was recorded in the Patent and Trademark Office on October 22, 1998 at Reel 009539, Frame 0550.

Related Appeals and Interferences

Appellant filed Appeal Briefs on October 10, 2003 for co-pending applications U.S. Serial Nos. 09/455,294 and 09/731,375 that address some issues that overlap with the issues presented here. Appellant also expects to file Appeal Briefs for co-pending applications U.S. Serial Nos. 09/141,220 and 09/494,096 addressing some issues that overlap with the issues presented here. No other pending appeals or interferences are known to Appellant, Appellant's legal representative, or Appellant's assignee that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no such pending appeals or interferences are known that may have a bearing on the Board's decision in this appeal.

Status of Claims

The application was filed with claims 1-36. Claims 1-13 were cancelled in a Preliminary Amendment filed January 6, 2000. Claims 14-36 were the subject of a Restriction Requirement mailed July 31, 2000. Claims 30-36 were cancelled September 29, 2000 in response to the Restriction Requirement. Claims 14-29 were examined in an Office Action mailed June 19, 2001. Claims 14-29 were canceled in an Amendment filed September 19, 2001; claims 37-59 were added. Claims 37-59 were finally rejected in an Office Action mailed December 18, 2001.

Claims 37-42, 46-47, 51 and 53 were amended in an Amendment filed June 18, 2002; claims 60-71 were added; and continued examination was requested under 37 C.F.R. § 1.114. Claims 37-71 were rejected in an Office Action mailed September 30, 2002. Thus, claims 37-71 are pending and stand rejected. The rejection of claims 37-71 is hereby appealed. A listing of pending claims 37-71 is provided as **Attachment I**.

Status of Amendments

The Original Brief was submitted with a proposed Amendment to the Claims that canceled claims 52 and 54-59 and amended claims 61-62 to correct an issue of antecedent basis. Appellant has not yet received an indication as to whether this Amendment has been entered. Appellant is therefore filing herewith a version of this earlier Amendment that includes an additional amendment to claim 63 that correct an obvious error in antecedent basis. A listing of claims 37-51, 53 and 60-71 that will be pending after entrance of the Amendment is provided as **Attachment II**. For the purpose of this Brief, Appellant is assuming that the Amendment will be entered since the claim amendments found therein simplify the issues under appeal. In particular, all rejections of claims 52 and 54-59 are rendered moot and antecedent basis in claims 61-63 is corrected. Accordingly, in the following the issues on appeal will be discussed as if they applied to the claims that will be pending *after* entrance of the Amendment. Appellant also submitted an Amendment to the Specification on February 19, 2004 that clarifies the priority claims in the present application.

Summary of Invention

The present invention is directed to modified protein allergens that have a reduced ability to bind IgE antibodies. The modified protein allergens have amino acid sequences that are substantially identical to those of unmodified protein allergens except that at least one amino acid has been modified in at least one IgE epitope. The modified protein allergens are useful in treating allergies and in particular anaphylactic allergies. The present specification includes data and working examples demonstrating the identification and modification of IgE epitopes from peanut allergens Ara h 1, Ara h 2 and Ara h 3 (see Examples 1-2). *In vitro* (see Examples 3-4) and *in vivo* (see Example 5) experiments that were performed with a modified Ara h 2 protein are also discussed. The specification also describes other known protein allergens, including a range of food allergens, that can be modified according to the teachings of the invention.

Issues

The issues on appeal are (referring to §§ **4-18** of Paper 24):

(1) Are the pending claims invalid for lack of enablement (see § **4**)?

(2) Are the pending claims invalid for lack of written description? Specifically, can the written description requirement ever be satisfied for claims relating to proteins without an explicit recitation in the specification of every sequence encompassed by the claims (see § **5**)?

(3) Are claims 65-69 invalid for containing new matter (see § **6**)?

(4) Are claims 37, 60 and 63 indefinite for reciting the term "substantially" (see § **8**)?

(5) Are claims 37-39, 41-46, 48-51 and 53 anticipated by U.S. Pat. 5,547,669 (see § **10**)?

(6) Are claims 37, 60-61 and 63-71 anticipated by Burks (1997) (see § **13**)?

(7) Are claims 37 and 47 obvious in light of U.S. Pat. 5,547,669 and Hoyne (see § **16**)?

(8) Is claim 37 obvious in light of U.S. Pat. 5,547,669 and Burks (1994) (see § **17**)?

(9) Are claims 60-62 obvious in light of U.S. Pat. 5,547,669 or Burks (1997) each in combination with U.S. Pat. 5,449,669 (see § **18**)?

Grouping of Claims

For ease of discussion, Appellant defines the following groups of claims (A)-(C):

(A) Claims 37-51, 53 and 65-71 as dependent from claim 37 that recite a modified protein allergen.

(B) Claims 60-62 and 65-71 as dependent from claim 60 that recite a modified **food** allergen.

(C) Claims 63-64 and 65-71 as dependent from claim 63 that recite a modified **peanut** allergen.

The claims stand or fall together for issues numbered (1)-(9) above, as indicated below:

(1) The claims of Group A stand or fall together. The claims of Groups B and C stand or fall together.

(2) The claims of Group A stand or fall together; the claims of Group B stand or fall together; and the claims of Group C stand or fall together.

(3) Claims 65-69 stand or fall together.

(4) Claims 37, 60 and 63 stand or fall together.

(5) Claims 37-39, 41-46, 48-51 and 53 stand or fall together.

(6) Claims 37, 60-61 and 63-71 stand or fall together.

(7) Claims 37 and 47 stand or fall together.

(8) Claim 37 stands or falls alone.

(9) Claims 60-62 stand or fall together.

Argument

ISSUE 1: Claims 37-51, 53 and 60-71 are not Invalid for Lack of Enablement

Claims 37-51, 53 and 60-71 stand rejected for lack of enablement (see § 4 of Paper 24). With respect to this rejection, the claims of Group A stand or fall together; and the claims of Groups C and D stand or fall together. In supporting this rejection, the Examiner cites *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and states that the disclosure in the specification is insufficient to enable one skilled in the art to practice the broader claimed invention without an undue amount of experimentation. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The Examiner begins the rejection by listing twenty different embodiments that she concedes **are** enabled by the specification including (see pages 2-4 of Paper 24):

(1) a modified *peanut* protein allergen whose amino acid sequence is identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein, [...]. This language parallels **claim 63** except for the "*substantially* identical" language that is addressed under Issue # 4 below.

(2)-(14) the modified *peanut* protein allergen of (1) further including certain limitations found in dependent **claims 38-51**.

(15) the modified *peanut* protein allergen of (1) made by the process of **claim 53**.

(16) a modified *food* allergen whose amino acid sequence is identical to that of an unmodified peanut [sic] protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified protein, [...]. This language parallels **claim 60** except for the "*substantially* identical" language that is addressed under Issue # 4 below.

(17) the modified *food* allergen of (16) wherein the unmodified food allergen is obtained from a source of *legumes*.

(18) a modified *peanut* allergen whose amino acid sequence is identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allege [sic] is reduced as compared with IgE binding to the unmodified peanut allergen, [...]. This language again parallels **claim 63** except for the "*substantially* identical" language that is addressed under Issue # 4 below.

(19) the modified *peanut* allergen of (18) wherein the unmodified peanut allergen is selected from the group consisting of Ara h 1, Ara h 2 and Ara h 3. This language parallels **claim 64**.

(20) the modified peanut allergen of (18) wherein the at least one IgE epitope contains at least one amino acid that residues [sic] that is modified as compared with the unmodified peanut allergen for immunotherapy. This language parallels **claims 65-70**.

The Examiner has therefore conceded that, other than the term "*substantially*", the claims of Groups C and D (i.e., claims 60-71 as dependent from claims 60 or 63) are enabled. Appellant addresses the term "*substantially*" under Issue # 4 below. With respect to this rejection, the claims of Groups C and D therefore stand or fall together.

Appellant respectfully submits that the claims of Group A are also enabled and that these claims stand or fall together for the following reasons. In light of the Examiner's concessions, Appellant notes that the only disputed enablement issue in this case is whether, in light of the teachings of the specification, undue experimentation is required to obtain modified protein allergens *other than* modified **food** and **peanut** allergens. In this context, Appellant and the Examiner agree that *Wands* is the relevant precedent. The question, therefore, is whether the experimentation required to obtain the broader claimed modified allergens would be more burdensome or complex, or less likely to result in success, than the experimentation required in *Wands*. If not, the inventors are entitled to allowance of the disputed claims. The answer to this question is obtained by comparison of the experimental procedures in the two cases. We begin by summarizing *Wands*.

In re Wands

In *Wands*, the inventors developed a diagnostic for the Hepatitis B virus. In particular, the inventors identified a particular antibody that bound to a viral protein and could, therefore, be used to determine whether the virus was present. In *Wands*, the claims were broad enough to encompass both the particular antibodies described in the specification and other antibodies

having the same or similar characteristics. The broadest claim encompassed any monoclonal, high affinity IgM antibody "having a binding affinity constant [...] of at least 10^9 M^{-1}." The specification described work by the inventors that led to the production of four antibodies falling within the scope of the claim. One hybridoma (a cell fusion that produces a single antibody) was deposited with the ATCC. Thus, the specification exemplified, at most, four antibodies that fell within the claim. The claim, however, encompassed all antibodies having the recited characteristics – a potentially infinite number of antibodies.

The Examiner rejected the Wands claim as too broad. He said that the disclosure in the specification was not commensurate in scope with the claim, that "the production of high Affinity IgM [...] antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies." *Id.* at 735.

The Federal Circuit reversed the Examiner (and the Board of Appeals). The Court held that the identification and production of other embodiments of the invention could have been achieved without undue experimentation. The Court said that "[a] patent need not disclose that which is well known in the art." *Id.* at 735. The Court held that the generic claims should have been allowed because (1) the starting materials necessary to obtain the generically described (i.e., non-exemplified) antibodies were available to the public, (2) the methods used to generate antibodies and to screen them to determine which fall within the claims were well known in the art, and (3) useful antibodies could therefore be obtained without undue experimentation.

The case turned on the concept of undue experimentation. The Court said that a "considerable amount of experimentation is permissible, if it is merely routine." *Id.* at 737. The Court then described the experimental procedure that would have been followed by scientists attempting to produce antibodies that were not expressly described in the *Wands* specification but that fell within the generic claims of the *Wands* application:

1. "The first step [...] is to immunize an animal." (p. 737)

2. "Next the [mouse's] spleen [...] is removed and the lymphocytes [in the spleen] are separated from the other spleen cells." (p. 737)

3. "The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other, thus creating hybridomas." (p. 737)

4. "Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening

procedures [of which] the first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells." (p. 737)

5. "The next step [of the screening procedures] is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide." (p. 737)

6. "After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen." (pp. 737-738)

7. Antibodies that fall within the claims are selected by determination of their "numerical affinity constant, which must be measured using the [...] laborious Scotchard analysis." (p. 738)

8. There is then performed "further screening to select those [antibodies] which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}." (p. 738)

The *Wands* inventors used these techniques. Some fusions were unsuccessful and produced no hybridomas; others produced hybridomas that made antibodies to the Hepatitis B surface antigen. Certain of these antibodies were screened. Some of the screened antibodies fell within the claims; others did not.

<u>No undue experimentation in *Wands*</u>

Despite the fact that a substantial amount of experimentation was required in *Wands* to obtain antibodies which were within the scope of the claims, the Court concluded that the experimentation was not "undue" and that the generic claims of the Wands patent were adequately enabled. The Court found that "there was a high level of skill in the art [...] and all of the methods needed to practice the invention were well-known." *Id.* at 740. The Court also found that, although the technology involved screening hybridomas to determine which, if any, secreted antibodies with the desired characteristics, "[p]ractitioners of the art [were] prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id.* at 740. The Court did not quantify the required likelihood of success, but noted that even a success rate as low as 2.8% would not necessarily require a conclusion of undue experimentation. *Id.* at 740.

<u>This case is similar to *Wands*</u>

As mentioned earlier, and as acknowledged by the Examiner, the present application provides explicit exemplification of modified peanut allergens that fall within the scope of

claims. The present application clearly states that its teachings are also applicable to other non-peanut allergens (e.g., see pages 7-9). The present application clearly sets forth all the steps necessary to identify and prepare suitable modified protein allergens that fall within the scope of the broadest claims, namely using patient sera to identify IgE binding epitopes; modifying a protein allergen sequence to alter identified IgE binding epitopes; and screening modified protein allergens to identify those with reduced binding. It is further undisputed that the sequences of numerous non-peanut protein allergens were known at the time of filing (a number of these are highlighted in the specification, e.g., see pages 7-9; others were known as evidenced by the numerous references and accession numbers that are provided in the "Official list of allergens," maintained by the IUIS Allergen Nomenclature Subcommittee and provided as **Attachment III**). For some of these protein allergens IgE binding sites were also already known (e.g., see page 8, lines 4-13). In addition, methods of identifying and modifying IgE binding sites were known and further described in the specification (e.g., see Examples 1 and 2). Those skilled in the art were also familiar with the methods that were used by the inventors to screen modified protein allergens for IgG and IgE binding and T-cell stimulation (e.g., see Examples 3 and 4).

At the time the application was filed, the starting materials necessary to obtain modified protein allergens were therefore available and the techniques for performing the necessary steps were well known and routine. Appellant respectfully submits that now that the inventors have demonstrated that the inventive methods *can* successfully be applied to protein allergens (i.e., that it is possible to generate modified protein allergens to which IgE binding is reduced but other characteristics remain unchanged), those skilled in the art would instantly realize that modified protein allergens derived from other allergens (1) would exist, (2) would operate in the same way to produce the same or similar results and (3) could be obtained using the techniques described in the application or which were well-known (indeed, routine) in the art.

The Examiner has presumably recognized this by conceding that the specification is enabling for *food* allergens in general (see (16) on page 3 of Paper 24). However, there is no particular magic in the sequence of peanut or food allergens that makes these protein allergens more susceptible to the inventive methods; the inventive principles, as discussed in the present application, apply to other protein allergens as well. In fact, quite the opposite might be expected. Peanut proteins are highly allergenic and, like many other food allergens (as distinguished, for example from most pollens and danders) present a significant risk of

anaphylaxis to those allergic to them. The inventive demonstration that such anaphylactic proteins can be modified so that IgE binding is reduced as compared with the unmodified allergens provides a strong teaching to those of ordinary skill in the art that other modified allergens with reduced IgE binding can also be made.

<u>Others have prepared modified allergens according to the teachings of the application without undue experimentation</u>

As further evidence that the claimed modified allergens may be obtained without undue experimentation, Appellant has identified a series of references showing that, after the present invention was made, people of ordinary skill in the art followed the steps taught in the present application (i.e., used patient sera to identify IgE binding epitopes, modified the protein sequence to alter identified IgE binding epitopes; and screened modified proteins to identify those with reduced binding) and were able to obtain, without undue experimentation, a variety of modified protein allergens that lie within the scope of the pending claims. More specifically, the following post-art references (already made of record in the Supplemental Response to Final Office Action that was filed September 19, 2002) were identified:

A. Timothy grass pollen allergen

Schramm et al., "Allergen engineering: variants of the Timothy grass pollen allergen Phl p 5b with reduced IgE-binding capacity but conserved T cell reactivity", *J. Immunol.*, 162:2406-2414, 1999.

B. English walnut allergen

Robotham et al., "Linear IgE epitope mapping of the English walnut (*Juglans regia7*) major food allergen, Jug r 1", *J. Allergy Clin. Immunol.* 109:143-149, 2002.

C. Latex allergen

Beezhold et al., "Mutational analysis of the IgE epitopes in the latex allergen Hev b 5", *J. Allergy Clin. Immunol.* 107:1069-1076, 2001.

D. Ryegrass pollen allergen

Swoboda et al., "Mutants of the major ryegrass pollen allergen Lol p 5, with reduced IgE-binding capacity: candidates for grass pollen-specific immunotherapy", *Eur. J. Immunol.* 32:270-280, 2002.

E. Potato allergen

Astwood et al., "Identification and characterization of IgE binding epitopes of patatin, a major food allergen of potato", *J. Allergy Clin. Immunol.* 105:S184 (Abstract 555), 2000.

F. Soybean allergen

Helm et al., "Mutational analysis of the IgE-binding epitopes of P34/Gly m Bd 30K", *J. Allergy Clin. Immunol.* 105:378-384, 2000.

G. Shrimp allergen

Ayuso et al., "Identification and mutational analysis of major epitopes of the shrimp allergen Pen a 1 (Tropomyosin)", *J. Allergy Clin. Immunol.* 105:S140 (Abstract 423), 2000.

Lehrer et al., "Current understanding of food allergens", *Ann. N.Y. Acad. Sci.* 964:69-85, 2002.

Appellant respectfully submits that this evidence reinforces the fact that there is no particular magic in the sequence of peanut or food allergens that makes these allergens more susceptible to mutation; the inventive principles, once demonstrated may be readily applied to other protein allergens.

<u>The Examiner's arguments fail to establish a case for lack of enablement</u>

Appellant acknowledges the arguments that have been made by the Examiner (i.e., see pages 7-10 of Paper 4). In particular, the Examiner cites various references that include a discussion of mutated peptides that failed to exhibit reduced IgE binding (Burks et al. and Stanley et al.) or T-cell stimulation (Fasler et al.) as compared to wild-type peptides. The Examiner suggests that these failures highlight the lack of predictability in the preparation of suitable modified protein allergens. However, the Examiner fails to recognize that even though the possibility exists that the initial modification of IgE binding epitopes may *not* identify suitable modified proteins, as was the case in *Wands* (and also in Burks et al., Stanley et al. and Fasler et al.), practitioners would be prepared to test more than one modification and to screen for useful modified proteins. The present case need only meet the enablement standard that was set in *Wands*. Appellant respectfully submits that the standard has been met, reconsideration and withdrawal of the rejection for lack of enablement is therefore requested.

ISSUE 2: Claims 37-51, 53 and 60-71 are not Invalid for Lack of Written Description

Claims 37-51, 53 and 60-71 stand rejected for lack of written description (see § **5** of Paper 24). With respect to this rejection, the claims of Group A stand or fall together; the claims of Group B stand or fall together; and the claims of Group C stand or fall together.

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Furthermore, there is a strong presumption that claims submitted with an application are adequately described by the application. *In re Wertheim* 541 F.2d 257 (Fed. Cir. 1993). Claims 37, 40-51 and 53 were present in substantially the same form as claims 14-29 in the application as originally filed. Added claims 60-64 parallel the language of claim 37 and are of narrower scope (i.e., they are simply limited to food or peanut allergens). Added claims 65-70 are dependent claims and recite the limitations found in original claim 14 and the data of Table 6 of the specification as filed (see discussion under Issue # 3 below). Added claim 71 is a dependent claim and recites a limitation found in the section spanning pages 24-25 of the specification as filed. The burden is therefore on the Examiner to overcome the strong presumption of descriptive support with evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Examiner has not, and cannot meet this burden; the claimed invention is appropriately described in the specification.

Both in her written rejections and in an in-person interview, the Examiner has indicated that, in her view, the written description requirement can never be satisfied for a nucleic acid or protein unless the complete sequence is explicitly set forth in the specification and recited in the claim by way of a SEQ ID NO. The same Examiner is responsible for the prosecution of a large number of related cases; we are unable to move prosecution forward without first resolving the question of whether the written description requirement can ever be satisfied without recitation of a SEQ ID NO. in the claim.

The absurdity of the Examiner's position is readily demonstrated by considering the modified peanut allergens that are exemplified in the specification and encompassed by the claims of Group C, which stand or fall together for the purposes of this rejection.

Claim 63, the only independent claim in Group C, recites:

> "A modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified peanut allergen is reduced as compared with IgE binding to the unmodified peanut allergen, the at least one IgE epitope being one that is recognized when the unmodified peanut allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut allergen."

The Examiner has rejected this claim on the ground that Appellant is only entitled to claim *full length* peanut allergens *Ara h 1, 2 and 3* that have been modified by substitution with *alanine* or *methionine* at those *specific locations* listed in Tables 4, 5 and 6 (see pages 13-14 of Paper 24). This is clearly not the law nor should it be. The proper legal question is not "did Appellant *reduce to practice* and *explicitly recite* every modified peanut allergen that falls within the scope of the claims?" Instead, the question is "would a skilled person recognize that Appellant was in *possession* of the modified peanut allergens that fall within the scope of the claims?"

The present specification sets forth the complete amino acid sequences of Ara h 1, 2, and 3 (SEQ ID NOs. 2, 4 and 6), and also the nucleotide sequences of genes that encode them (SEQ ID NOs. 1, 3 and 5). The specification further sets out the amino acid sequences of each of 23 IgE epitopes mapped in the Ara h 1 protein (Table 1), the amino acid sequence of each of 10 IgE epitopes mapped in the Ara h 2 protein (Table 2), and the amino acid sequence of each of 4 epitopes mapped in the Ara h 3 protein (Table 3). The specification further describes particular alanine or methionine substitutions that were introduced into the mapped IgE binding sites, and shows that some of these substitutions result in decreased IgE binding (Tables 4-6). In discussing these data, the specification states (see page 25, lines 11-23):

> "The results discussed above for Ara h 1, Ara h 2, and Ara h 3 demonstrate that once an IgE binding site has been identified, it is possible to reduce IgE binding to this site by altering a single amino acid of the epitope. [...] Besides finding that many epitopes contained more than one residue critical for IgE binding, it was also determined that more than one residue type (ala or met) could be substituted at certain positions in an epitope with similar results. This allows for the design of a hypoallergenic protein that would be effective at blunting allergic reactions for a population of peanut sensitive individuals."

Thus, the specification specifically highlights that substitutions at different positions, and with different amino acids, achieved the same results.

The Examiner is correct that the specification does not explicitly set forth the sequences of all possible disruptions to Ara h 1, Ara h 2, and Ara h 3 IgE sites. However, a skilled person, reading the specification, would understand, indeed would explicitly be told, that the presented substitutions were merely exemplary and others would work as well. A skilled artisan would appreciate that the techniques described in the specification would successfully identify all such substitutions. That is, a skilled person would understand that the inventors were in *possession* of the invention to the full scope of claim 63.

A claim limited to the particular substitutions that the inventors happened to have made prior to filing their patent application is virtually useless. Anybody of ordinary skill in the art could prepare an altered allergen that falls outside the scope of the claim but still embodies the spirit, scope, and teachings of Appellant's contribution. If the legal standard of written description in fact required verbatim recitation of every possible useful sequence, as asserted by the Examiner, patent applicants would be forced to perform useless and wasteful experiments (potentially endlessly) merely to ensure that they could protect their contributions. Such a standard would eviscerate the patent system. The Examiner's rejection of Group C claims for lack of written description should be removed.

The Examiner's rejection of Group B claims for lack of written description should also be removed. Claim 60, the only independent claim in this group, recites:

> "A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen."

Once again, the Examiner is correct that the specification does not explicitly set out the sequence of every modified food allergen that falls within the scope of claim 60. On the other hand, as discussed above, the specification does explicitly set out the sequence of several examples of modified peanut allergens. These modified peanut allergens are described as "exemplary" of the inventive principles. For example, the specification recites that "Peanut allergens (Ara h 1, Ara h

2, and Ara h 3) have been used in the examples to demonstrate alteration of IgE binding sites while retaining binding to IgG and activation of T cells" (page 4, lines 15-17). The specification also points to several other common food allergens (see page 8, lines 1-3: "Examples of common food allergens include proteins from peanuts, milk, grains such as wheat and barley, soybeans, eggs, fish, crustaceans, and mollusks."). Moreover, the specification provides references for food allergens *whose IgE epitopes had already been* identified (see page 8, lines 4-13). The specification also describes techniques for modifying sequences within IgE sites (see, for example, page 10, lines 3-6 and Examples 2-3), and for identifying those modifications that reduce IgE binding (see, for example, page 4, lines 24-28 and Examples 1-2) in accordance with claim 60.

And, of course, the specification provides evidence that the inventive strategy successfully produced modified peanut allergens with reduced IgE reactivity. The teachings and guidance provided by this success are far-reaching. As discussed above and in the specification, peanut allergy is one of the most potent allergies. Indeed, as noted in the specification (see page 16, lines 4-11):

> "Peanut allergy is one of the most common and serious of the immediate hypersensitivity reactions to foods in terms of persistence and severity of reaction. [...] The majority of cases of fatal food-induced anaphylaxis involve ingestion of peanuts [...]."

A person of ordinary skill in the art would immediately understand the exciting implications of the inventive exemplification of reduced-allergenicity peanut allergens: if it works for peanuts, it will work for other food allergens.

The claimed food allergens are all proteins; sensitized individuals are exposed to them all by the same route (i.e., ingestion); they are all readily modified according to the same techniques, and those with reduced allergenicity are identified in the same manner. Reading the present specification, those of ordinary skill in the art will immediately appreciate that modified food allergens with reduced allergenicity, according to the present claims, exist, and can readily be made according to the teachings of the specification. In other words, those of ordinary skill in the art will immediately appreciate that the inventors were *in possession of* the claimed invention. Denial of claims to modified food allergens would deprive the present inventors of protection commensurate in scope with their contribution, and would create silly incentives

disruptive to science, the patent process, and commerce. For all of these reasons, the Examiner's rejection of claims in Group B for lack of written description, should be removed.

The rejection for lack of written description should also be removed for the claims of Group A, which stand or fall together for the purposes of this rejection. These claims are broader than those of Groups B and C in that they do not limit the category of protein allergen whose IgE epitopes are modified. Although the claims are broad, there is no failure of written description.

The specification makes clear that the inventive principles are applicable to *any* allergen (see, for example, page 4, lines 2-14; page 7, line 26 to page 9, line 15; and page 29, lines 18-20). The specification also specifically lists a variety of relevant allergens (see, for example, page 8, lines 13-16: "Other allergens include proteins from insects such as flea, tick, mite, fire ant, cockroach, and bee as well as molds, dust, grasses, trees, weeds, and proteins from mammals including horses, dogs, cats, etc."). The specification includes extensive discussion of latex allergens, in particular, and provides references reporting IgE epitopes within these allergens (see, for example, page 8, line 19-page 9, line 15). The specification further recites the specific modifications of claims 38-42 (e.g., see page 4, lines 17-23 and the Examples) and the properties of claims 43-45 (e.g., see page 4, lines 8-14 and 26-28). The specification also specifically recites relevant subsets of antigens recited in claims 51 and 60-62 (e.g., pages 7-9 and the Examples). Likewise, the specification specifically points to adjuvants having the characteristics recited in claim 47 (e.g., see page 15, lines 19-20) and to recombinantly prepared modified allergens as recited in claims 48-50 (e.g., see page 12 and Example 3). The steps of claim 53 are described on pages 9-10 and in the Examples.

All of this information explicitly set forth in the specification, combined with the potent demonstration of success with the most challenging allergens, clearly put the public on notice that the inventors were in possession of the invention to the full scope of the present claims.

Appellant appreciates that certain court decisions, including *University of California v. Eli Lilly and Co.* have been interpreted to stand for the proposition that, in certain cases, nucleic acid or protein molecules cannot be properly described in a patent specification without explicit recitation of sequence information. However, this is not such a case. First, significant sequence information *is* provided for this case. Furthermore, a determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge

possessed by those skilled in the art *at the time that the invention was filed* (*In re Alton*, 76 F3d 1168, 37 USPQ 2d 1578 (Fed. Cir. 1996)). In *University of California v. Eli Lilly and Co.*, the patent applications in issue were filed in 1977 and 1979; the present application was filed 20 years later. A lot happened in the intervening 20 years. Automated sequencing and synthesis technologies were developed; PCR was invented; a variety of techniques for disrupting or otherwise mutagenizing a nucleic acid sequence were standardized. Mechanical application of a "Sequence Listing or bust" rule vitiates the very purpose of the *Lily* ruling, which was to ensure that the scope of patent claims was commensurate in scope with the contribution. The present specification describes the invention of particular modified protein allergens for a wide variety of allergens; the pending claims are of appropriate scope.

ISSUE 3: Claims 65-69 are not Invalid for Containing New Matter

The Examiner has questioned the support for the recitation in claims 65-69 of a modified protein allergen that comprises at least one IgE epitope with 1-6, 1-5, 1-4, 1-3 or 1-2 modified amino acid residues (see § **6** of Paper 24). With respect to this rejection claims 65-69 stand or fall together.

Appellant respectfully submits that these claims are fully supported by the specification and claims as originally filed. In particular, original claim 14 reads "a modified allergen [...] comprising at least one IgE binding site [...] modified by *at least one* amino acid change [...]." Original claim 14 therefore makes it perfectly clear that the present invention encompasses modified protein allergens with at least one IgE binding site that includes *more than one* modified amino acid residue. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively). The specification and claims as originally filed therefore clearly support the language of pending claims 65-69.

ISSUE 4: Claims 37, 60 and 63 are not Indefinite for Reciting the Term "Substantially"

The Examiner has taken the position that claims 37, 60 and 63 are indefinite under 35 U.S.C. § 112, second paragraph for reciting the term "substantially" without providing a definition of the term in the specification (see § **8** of Paper 24). With respect to this rejection claims 37, 60 and 63 stand or fall together.

Appellant respectfully disagrees with this rejection. The courts have clearly stated that expressions such as "substantially" may be used in patent claims when warranted by the nature of invention, in order to accommodate the minor variations that may be appropriate to secure the invention. *Verve LLC v. Crane Cams*, 311 F.3d 1116 (Fed. Cir. 2002). The nature of the presently claimed invention is such that minor variations from an otherwise "identical amino acid sequence" (e.g., the addition of a single terminal methionine during recombinant synthesis) could be made without losing the benefit of the present invention. One skilled in the art, upon reading the present specification, would readily recognize such trivial variations. No more is required. In fact, as noted in Judge Hand's opinion in *Musher Foundation v. Alba Trading Co.*, 326 U.S. 770 (1945):

> 'Substantially' is not of itself fatal to a claim [...] indeed, it must always be implied in every claim, even when not introduced, and adds nothing when it is. Were this not true, few patents could be given any protection, for some departures from the precise disclosure are nearly always possible without losing the benefit of the invention.

For all of these reasons, withdrawal of the rejection is earnestly requested.

ISSUE 5: Claims 37-39, 41-46, 48-51 and 53 are not anticipated by U.S. Pat. 5,547,669

The Examiner has rejected claims 37-39, 41-46, 48-51 and 53 under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat. 5,547,669 (see § **10** of Paper 24). This rejection is respectfully traversed; with respect to this rejection claims 37-39, 41-46, 48-51 and 53 stand or fall together.

As discussed in the Response to Office Action filed June 18, 2002, the "recombitope peptides" that are taught by U.S. Pat. 5,547,669 cannot anticipate these claims since they do not satisfy the limitations of every claimed element. In particular, one skilled in the art would immediately recognize that a "recombitope peptide" does *not* have an amino acid sequence that is "substantially identical to that of an unmodified allergen except that at least one amino acid has been modified in at least one IgE epitope."

In general, "recombitope peptides" are peptides that include at least two T-cell epitopes derived from the same or from different protein antigens (e.g., see Abstract). It is presumably undisputed that a "recombitope peptide" that includes T-cell epitopes derived from *different* protein antigens will necessarily have an amino acid sequence that bears no resemblance whatsoever to the amino acid sequence of either parent antigen. Further, when the T-cell

epitopes are from the *same* protein antigen we are taught that these should be arranged in a *noncontiguous configuration*, namely:

> "an arrangement of amino acids comprising T-cell epitopes [...] which is *different* than that of an amino acid sequence present in the protein allergen or other protein antigen from which the epitopes [...] are derived." (see lines 3-8, column 7, emphasis added).

and a *nonsequential* order, namely:

> "an order *different* from the order of the amino acids of the native protein allergen or other protein antigen from which the T-cell epitopes [...] are derived [...]." (e.g., see lines 8-14, column 7, emphasis added).

In order to reduce the likelihood of IgE binding, IgE epitopes are preferably *excluded* from the amino acid sequences of "recombitope peptides":

> "Those peptide regions found to bind immunoglobulin E and cause the release of mediators from mast cell or basophils in greater than approximately 10-15% of the allergic sera tested are *preferably not included* in the peptide regions arranged to form recombitope peptides". (e.g., see lines 5-9, column 8, emphasis added)

Again it is presumably undisputed that these "recombitope peptides" will also have an amino acid sequence that bears no resemblance to the amino acid sequence of the parent antigen. As the foregoing sections highlight, U.S. Pat. 5,547,669 teaches methods that involve extracting, rearranging and pasting T-cell epitopes that were originally present in one or more natural protein antigens. IgE epitopes are preferably extracted and removed entirely. The resultant "recombitope peptides" are wholly artificial peptides that bear no resemblance whatsoever to their parent antigen(s). U.S. Pat. 5,547,669 therefore teaches strongly *away* from modified protein allergens whose amino acid sequence is substantially *identical* to that of an unmodified protein allergen *except that* at least one amino acid has been modified in at least one IgE epitope of the unmodified protein allergen, as recited in the present claims. The substitutions, deletions, or additions that are referred to by the Examiner (e.g., lines 1-5, 15-17 and 59-62, column 15) do not remedy these deficiencies, if anything they further differentiate "recombitope peptides" from the claimed invention. U.S. Pat. 5,547,669 does not anticipate or render obvious claims 37-39, 41-46, 48-51 and 53. Withdrawal of the rejection is earnestly requested.

ISSUE 6: Claims 37, 60-61 and 63-71 are not anticipated by Burks (1997)

The Examiner has rejected claims 37, 60-61 and 63-71 under 35 U.S.C. § 102(a) as being anticipated by Burks et al. (*Eur. J. Biochem.* 245:334-339, 1997) (see § **13** of Paper 24). With respect to this rejection claims 37, 60-61 and 63-71 stand or fall together.

Appellant respectfully disagrees with the rejection and notes that the teachings of Burks (1997) were included near *verbatim* in U.S. Serial No. 08/717,933 filed September 23, 1996 (see pp. 133-155 and the Figures referred to therein). The present application properly claims priority to this 1996 filing. Burks (1997) was published after this priority date and cannot therefore be used as prior art under 35 U.S.C. § 102(a). Withdrawal of the rejection is earnestly requested.

ISSUE 7: Claims 37 and 47 are not obvious in light of U.S. Pat. 5,547,669 and Hoyne

The Examiner has rejected claims 37 and 47 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. 5,547,669 in view of Hoyne (*Immunology and Cell Biology* 74:180-186, 1996) (see § **16** of Paper 24). With respect to this rejection claims 37 and 47 stand or fall together. The teachings of U.S. Pat. 5,547,669 and its deficiencies with regards to independent claim 37 have been discussed *supra*. Hoyne is cited solely as teaching certain elements added in dependent claim 47, specifically certain adjuvants. The Examiner indicates no teaching or suggestion in Hoyne that could overcome the deficiencies of U.S. Pat. 5,547,669. Withdrawal of the rejection is earnestly requested.

ISSUE 8: Claim 37 is not obvious in light of U.S. Pat. 5,547,669 and Burks (1994)

The Examiner has rejected claim 37 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. 5,547,669 in view of Burks (*J. Allergy Clin. Immunol.* 93:743-750, 1994) (see § **17** of Paper 24). The teachings of U.S. Pat. 5,547,669 and its deficiencies with regards to claim 37 have been discussed *supra*. Burks (1994) is a secondary reference that is cited solely as teaching unmodified protein allergens, namely peanut Ara h 1 and Ara h 2, and alleged IgE epitopes of these. For the record, Appellant notes that Burks (1994) does *not* teach IgE epitopes of Ara h 2 and only identifies the existence of three IgE epitopes of Ara h 1 based on an ELISA inhibition assay using monoclonal antibodies – the locations of these three IgE epitopes within the Ara h 1 amino acid sequence are not provided. Besides, even if Burks (1994) had taught the location of any IgE epitope of Ara h 1 and/or Ara h 2, the Examiner has failed to point to any teaching or suggestion in Burks (1994) that could overcome the aforementioned deficiencies of U.S. Pat.

5,547,669. Withdrawal of the rejection is earnestly requested.

ISSUE 9: Claims 60-62 are not obvious in light of U.S. Pat. 5,547,669 or Burks (1997) each in combination with U.S. Pat. 5,449,669

The Examiner has rejected claims 60-62 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. 5,547,669 or Burks (1997) each in view of U.S. Pat. 5,449,669 (see § **18** of Paper 24). With respect to this rejection claims 60-62 stand or fall together. The teachings of U.S. Pat. 5,547,669 and its lackings have been discussed *supra*. As discussed *supra*, Burks (1997) is not available as prior art under 35 U.S.C. § 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of U.S. Pat. 5,547,669. Withdrawal of the rejection is earnestly requested.

Conclusion

Appellant again concludes with the belief that claims 37-51, 53 and 60-71 as amended by the Amendment filed herewith are fully supported by the specification as filed and allowable over the art of record. Allowance of these claims is earnestly requested.

Respectfully submitted,

Dated: March 23, 2004

Brenda Herschbach Jarrell, Ph.D.
Registration No. 39,223

PATENT DEPARTMENT
CHOATE, HALL & STEWART
Exchange Place
53 State Street
Boston, MA 02109
Telephone: (617) 248-5000
Facsimile: (617) 248-4000

Attachment I

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending before Entrance of Amendment

Claims Pending before Entrance of Amendment

37. **(Previously presented)** A modified protein allergen whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen.

38. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified protein allergen.

39. **(Previously presented)** The modified protein allergen of claim 37 wherein the at least one IgE epitope is one that is recognized when the unmodified protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the unmodified protein allergen.

40. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one modified amino acid is located in the center of the at least one IgE epitope.

41. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been modified by substitution.

42. **(Previously presented)** The modified protein allergen of claim 41 wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid.

43. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to activate T cells.

44. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to bind IgG.

45. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to initiate a Th1-type response.

46. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen is a portion of the unmodified protein allergen.

47. **(Previously presented)** A composition comprising the modified protein allergen of claim 37 and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ, and immune stimulatory sequences.

48. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen is made in a transgenic plant or animal.

49. **(Previously presented)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of plants and animals.

50. **(Previously presented)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells.

51. **(Previously presented)** The modified protein allergen of claim 37 wherein the unmodified protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes.

52. **(Previously presented)** The modified protein allergen of claim 37 wherein the natural protein allergen is a peanut protein selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

53. **(Previously presented)** The modified protein allergen of claim 37 made by the process of:

identifying at least one IgE epitope in an unmodified protein allergen;

preparing at least one modified protein allergen whose amino acid sequence is substantially identical to that of the unmodified protein allergen except, that at least one amino acid has been modified in the at least one IgE epitope;

screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified protein allergen; and

selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified protein allergen.

54. **(Previously presented)** In combination, a natural protein allergen and a masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen in such a way that IgE binding is reduced as compared with IgE binding to the natural protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen.

55. **(Previously presented)** The combination of claim 54 wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen.

56. **(Previously presented)** The combination of claim 54 wherein the masking compound is an antibody that binds non-covalently to the at least one IgE epitope.

57. **(Previously presented)** The combination of claim 54 wherein the combination retains the ability to activate T cells.

58. **(Previously presented)** The combination of claim 54 wherein the combination retains the ability to bind IgG.

59. **(Previously presented)** The combination of claim 54 wherein the combination retains the ability to initiate a Th1-type response.

60. **(Previously presented)** A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen.

61. **(Previously presented)** The modified protein allergen of claim 60 wherein the unmodified food allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.

62. **(Previously presented)** The modified protein allergen of claim 61 wherein the unmodified food allergen is obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.

63. **(Previously presented)** A modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the

modified peanut allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified peanut allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut allergen.

64. **(Previously presented)** The modified peanut allergen of claim 63 wherein the unmodified peanut allergen is selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

65. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-6 amino acid residues that are modified as compared with the unmodified allergen.

66. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-5 amino acid residues that are modified as compared with the unmodified allergen.

67. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-4 amino acid residues that are modified as compared with the unmodified allergen.

68. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-3 amino acid residues that are modified as compared with the unmodified allergen.

69. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-2 amino acid residues that are modified as compared with the unmodified allergen.

70. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1 amino acid residue that is modified as compared with the unmodified allergen.

71. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen.

Attachment II

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending after Entrance of Amendment

Claims Pending after Entrance of Amendment

37. **(Previously presented)** A modified protein allergen whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen.

38. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified protein allergen.

39. **(Previously presented)** The modified protein allergen of claim 37 wherein the at least one IgE epitope is one that is recognized when the unmodified protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the unmodified protein allergen.

40. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one modified amino acid is located in the center of the at least one IgE epitope.

41. **(Previously presented)** The modified protein allergen of claim 37 wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been modified by substitution.

42. **(Previously presented)** The modified protein allergen of claim 41 wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid.

43. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to activate T cells.

44. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to bind IgG.

45. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to initiate a Th1-type response.

46. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen is a portion of the unmodified protein allergen.

47. **(Previously presented)** A composition comprising the modified protein allergen of claim 37 and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ, and immune stimulatory sequences.

48. **(Previously presented)** The modified protein allergen of claim 37 wherein the modified protein allergen is made in a transgenic plant or animal.

49. **(Previously presented)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of plants and animals.

50. **(Previously presented)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells.

51. **(Previously presented)** The modified protein allergen of claim 37 wherein the unmodified protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes.

52. **(Canceled)**

53. **(Previously presented)** The modified protein allergen of claim 37 made by the process of:

identifying at least one IgE epitope in an unmodified protein allergen;

preparing at least one modified protein allergen whose amino acid sequence is substantially identical to that of the unmodified protein allergen except, that at least one amino acid has been modified in the at least one IgE epitope;

screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified protein allergen; and

selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified protein allergen.

54-59. **(Canceled)**

60. **(Previously presented)** A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen.

61. **(Currently amended)** The modified food allergen of claim 60 wherein the unmodified food allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.

62. **(Currently amended)** The modified food allergen of claim 61 wherein the unmodified food allergen is obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.

63. **(Currently amended)** A modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified peanut allergen is reduced as compared with IgE binding to the unmodified peanut allergen, the at least one IgE epitope being one that is recognized when the unmodified peanut allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut allergen.

64. **(Previously presented)** The modified peanut allergen of claim 63 wherein the unmodified peanut allergen is selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

65. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-6 amino acid residues that are modified as compared with the unmodified allergen.

66. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-5 amino acid residues that are modified as compared with the unmodified allergen.

67. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-4 amino acid residues that are modified as compared with the unmodified allergen.

68. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-3 amino acid residues that are modified as compared with the unmodified allergen.

69. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-2 amino acid residues that are modified as compared with the unmodified allergen.

70. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1 amino acid residue that is modified as compared with the unmodified allergen.

71. **(Previously presented)** The modified allergen of claim 37, claim 60, or claim 63, wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen.

Attachment III

to

Appeal Brief under 37 C.F.R. § 1.192

<u>"Official list of allergens" maintained by the IUIS Allergen Nomenclature Subcommittee printed on June 8, 2003 from ftp://biobase.dk/pub/who-iuis/allergen.list</u>

Official list of allergens
IUIS Allergen Nomenclature Subcommittee
ftp://biobase.dk/pub/who-iuis/allergen.list

2000.03.01 Jorgen Nedergaard Larsen and Henning Lowenstein,
ALK-Abello, Boge Alle 6-8, DK-2970 Horsholm, Denmark
Please report changes, additions or comments to jnlarsen@inet.uni2.dk

Legends: MW determined by reducing SDS-PAGE; asterisk: MW deduced from sequence;
C: cDNA seq; P: peptide seq;

Allergen source	Systematic and original names	MW kDa	sequence data	Accession # or References
A. Weed pollens				
Asterales				
Ambrosia artemisiifolia				
(short ragweed)	Amb a 1; antigen E	38	C	8,20
	Amb a 2; antigen K	38	C	8,21
	Amb a 3; Ra3	11	C	22
	Amb a 5; Ra5	5	C	11,23
	Amb a 6; Ra6	10	C	24,25
	Amb a 7; Ra7	12	P	26
	Amb a ?	11	C	27
Ambrosia trifida				
(giant ragweed)	Amb t 5; Ra5G	4.4	C	9,10,28
Artemisia vulgaris				
(mugwort)	Art v 1;	27-29	C	28A
	Art v 2;	35	P	29
Helianthus annuus				
(sunflower)	Hel a 1;	34	-	29a
	Hel a 2; profilin	15.7	C	Y15210
Mercurialis annua				
	Mer a 1; profilin	14-15	C	Y13271
B. Grass pollens				
Poales				
Cynodon dactylon				
(Bermuda grass)	Cyn d 1;	32	C	30,S83343
	Cyn d 7;		C	31,X91256
	Cyn d 12; profilin	14	C	31a,Y08390
Dactylis glomerata				
(orchard grass)	Dac g 1; AgDg1	32	P	32
	Dac g 2;	11	C	33,S45354
	Dac g 3;		C	33a,U25343
	Dac g 5;	31	P	34
Holcus lanatus				
(velvet grass)	Hol l 1;		C	Z27084,Z68893

Lolium perenne				
(rye grass)	Lol p 1; group I	27	C	35,36
	Lol p 2; group II	11	C	37,37a,X73363
	Lol p 3; group III	11	C	38
	Lol p 5; Lol p IX, Lol p Ib	31/35	C	34,39
	Lol p 11; trypsin inh. Related	16		39a
Phalaris aquatica				
(canary grass)	Pha a 1;		C	40,S80654
Phleum pratense				
(timothy)	Phl p 1;	27	C	X78813
	Phl p 2;		C	41,X75925
	Phl p 4;		P	41A
	Phl p 5; Ag25	32	C	42
	Phl p 6;		C	43,Z27082
	Phl p 12; profilin		C	44,X77583
	Phl p 13; polygalacturonase	55-60	C	AJ238848
Poa pratensis				
(Kentucky blue	Poa p 1; group I	33	P	46
grass)	Poa p 5;	31/34	C	34,47
Sorghum halepense				
(Johnson grass)	Sor h 1;		C	48

C. Tree pollens

Fagales:

Alnus glutinosa				
(alder)	Aln g 1;	17	C	S50892
Betula verrucosa				
(birch)	Bet v 1;	17	C	see iso-list
	Bet v 2; profilin	15	C	M65179
	Bet v 3;		C	X79267
	Bet v 4;	8	C	X87153/S54819
	Bet v 6; isoflavone reductase homologue	33.5	C	AF135127
	Bet v 7; cyclophilin	18	P	P81531
Carpinus betulus				
(hornbeam)	Car b 1;	17	C	see iso-list
Castanea sativa				
(chestnut)	Cas s 1; Bet v 1 homologue	22	P	52
	Cas s 5; chitinase			
Corylus avellana				
(hazel)	Cor a 1;	17	C	see iso-list
Quercus alba				
(white oak)	Que a 1;	17	P	54

Lamiales:

Oleaceae:				
Fraxinus excelsior (ash)	Fra e 1;	20	P	58A
Ligustrum vulgare (privet)	Lig v 1;	20	P	58A
Olea europea (olive)	Ole e 1;	16	C	59,60
	Ole e 2; profilin	15-18	C	60A
	Ole e 3;	9.2		60B
	Ole e 4;	32	P	P80741
	Ole e 5; superoxide dismutase	16	P	P80740
	Ole e 6;	10	C	U86342
	Ole e 7;	?	P	P81430
Syringa vulgaris (lilac)	Syr v 1;	20	P	58A
Plantaginaceae:				
Plantago lanceolata (English plantain)	Pla l 1;	18	P	P842242
Pinales:				
Cryptomeria japonica (sugi)	Cry j 1;	41-45	C	55,56
	Cry j 2;		C	57, D29772
Cupressus arizonica (cypress)	Cup a 1;	43	C	A1243570
Juniperus ashei (mountain cedar)	Jun a 1;	43	P	P81294
	Jun a 3;	30	P	P81295
Juniperus oxycedrus (prickly juniper)	Jun o 2; calmodulin-like	29	C	AF031471
Juniperus sabinoides (mountain cedar)	Jun s 1;	50	P	58
Juniperus virginiana (eastern red cedar)	Jun v 1;	43	P	P81825
D. Mites				
Acarus siro (mite)	Aca s 13; fatty acid-bind.prot.	14*	C	AJ006774
Blomia tropicalis (mite)	Blo t 5;		C	U59102
	Blo t 12; Bt11a		C	U27479
	Blo t 13; Bt6 fatty acid-binding prot.		C	U58106

Dermatophagoides pteronyssinus				
(mite)	Der p 1; antigen P1	25	C	61
	Der p 2;	14	C	62
	Der p 3; trypsin	28/30	C	63
	Der p 4; amylase	60	P	64
	Der p 5;	14	C	65
	Der p 6; chymotrypsin	25	P	66
	Der p 7;	22-28	C	67
	Der p 8; glutathione transferase		C	67A
	Der p 9; collagenolytic serine prot.		P	67B
	Der p 10; tropomyosin	36	C	Y14906
	Der p 14; apolipophorin like p.		C	Epton p.c.
Dermatophagoides microceras				
(mite)	Der m 1;	25	P	68
Dermatophagoides farinae				
(mite)	Der f 1 ;	25	C	69
	Der f 2 ;	14	C	70,71
	Der f 3 ;	30	C	63
	Der f 10; tropomyosin		C	72
	Der f 11; paramyosin	98	C	72a
	Der f 14; Mag3, apolipophorin		C	D17686
Euroglyphus maynei				
(mite)	Eur m 14; apolipophorin	177	C	AF149827
Lepidoglyphus destructor				
(storage mite)	Lep d 2.0101;	15	C	73,74,75
	Lep d 2.0102;	15	C	75
E. Animals				
Bos domesticus				
(domestic cattle)	Bos d 2; Ag3,lipocalin	20	C	76,L42867
(see also foods)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77
	Bos d 8; caseins	20-30		77
Canis familiaris				
(Canis domesticus)	Can f 1;	25	C	78,79
(dog)	Can f 2;	27	C	78,79
	Can f ?; albumin		C	S72946
Equus caballus				
(domestic horse)	Equ c 1; lipocalin	25	C	U70823
	Equ c 2; lipocalin	18.5	P	79A, 79B
Felis domesticus				
(cat saliva)	Fel d 1; cat-1	38	C	15
Mus musculus				
(mouse urine)	Mus m 1; MUP	19	C	80,81

Rattus norvegius (rat urine)	Rat n 1	17	C	82,83

F. Fungi

1. Ascomycota

1.1 Dothidiales

Alternaria alternata				
	Alt a 1;	28	C	U82633
	Alt a 2;	25	C	
	Alt a 3; heat shock prot. 70		C	U87807, U87808
	Alt a 4; prot.disulfidisomerase	57	C	X84217
	Alt a 6; acid.ribosomal prot P2	11	C	X78222, U87806
	Alt a 7; YCP4 protein	22	C	X78225
	Alt a 10; aldehyde dehydrogen.	53	C	X78227, P42041
	Alt a 11; enolase	45	C	U82437
	Alt a 12;acid.ribosomal prot P1	11	C	X84216
Cladosporium herbarum				
	Cla h 1;	13		83a, 83b
	Cla h 2;	23		83a, 83b
	Cla h 3; aldehyde dehydrogenase	53	C	X78228
	Cla h 4; acid.ribosomal prot P2	11	C	X78223
	Cla h 5; YCP4 protein	22	C	X78224
	Cla h 6; enolase	46	C	X78226
	Cla h 12;acid.ribosomal prot P1	11	C	X85180

1.2 Eurotiales

Aspergillus flavus				
	Asp fl 13; alkaline serine proteinase	34		84
Aspergillus fumigatus				
	Asp f 1;	18	C	M83781,S39330
	Asp f 2;	37	C	U56938
	Asp f 3; peroxisomal protein	19	C	U20722
	Asp f 4;	30	C	AJ001732
	Asp f 5; metalloprotease	42	C	Z30424
	Asp f 6; Mn superoxide dismutase	26.5	C	U53561
	Asp f 7;	12	C	AJ223315
	Asp f 8; ribosomal protein P2	11	C	AJ224333
	Asp f 9;	34	C	AJ223327
	Asp f 10; aspartic protease	34	C	X85092
	Asp f 11; peptidyl-prolyl isom	24		84a
	Asp f 12; heat shock prot. P90	90	C	85
	Asp f 13; alkaline serine proteinase	34		84b
	Asp f 15;	16	C	AJ002026
	Asp f 16;	43	C	g3643813
	Asp f 17;		C	AJ224865
	Asp f 18; vacuolar serine proteinase	34		84c

Aspergillus niger				
	Asp n 14; beta-xylosidase	105	C	AF108944
	Asp n 18; vacuolar serine proteinase	34	C	84b
	Asp n ?;	85	C	Z84377
Aspergillus oryzae				
	Asp o 13; alkaline serine proteinase	34	C	X17561
	Asp o 21; TAKA-amylase A	53	C	D00434,M33218
Penicillium brevicompactum				
	Pen b 13; alkaline serine Proteinase	33		86a
Penicillium citrinum				
	Pen c 3; peroxisomal membrane protein	18		86b
	Pen c 13; alkaline serine proteinase	33		86a
	Pen c 19; heat shock prot. P70	70	C	U64207
Penicillium notatum				
	Pen n 13; alkaline serine proteinase	34		89
	Pen n 18; vacuolar serine proteinase	32		89
	Pen n 20; N-acetyl glucosaminidase	68		87
Penicillium oxalicum				
	Pen o 18; vacuolar serine proteinase	34		89
1.3 Onygenales				
Trichophyton rubrum				
	Tri r 2;		C	90
	Tri r 4; serine protease		C	90
Trichophyton tonsurans				
	Tri t 1;	30	P	91
	Tri t 4; serine protease	83	C	90
1.4 Saccharomycetales				
Candida albicans				
	Cand a 1;	40	C	88
Candida boidinii				
	Cand b 2;	20	C	J04984, J04985
2 Basidiomycota				
2.1 Basidiolelastomycetes				
Malassezia furfur				
	Mala f 1;			91a

	Mala f 2; MF1 peroxisomal membrane protein	21	C	AB011804
	Mala f 3; MF2 peroxisomal membrane protein	20	C	AB011805
	Mala f 4;	35	C	Takesako,p.c.
	Mala f 5;	18*	C	AJ011955
	Mala f 6; cyclophilin homologue	17*	C	AJ011956
2.2 Basidiomycetes				
Psilocybe cubensis				
	Psi c 1;			
	Psi c 2; cyclophilin	16		91b
Coprinus comatus (shaggy cap)	Cop c 1; leucine zipper prot.	11	C	AJ132235
	Cop c 2;			Brander,p.c.
	Cop c 3;			Brander,p.c.
	Cop c 5;			Brander,p.c.
	Cop c 7;			Brander,p.c.
G. Insects				
Aedes aegyptii (mosquito)	Aed a 1; apyrase	68	C	L12389
	Aed a 2;	37	C	M33157
Apis mellifera (honey bee)	Api m 1; phospholipase A2	16	C	92
	Api m 2; hyaluronidase	44	C	93
	Api m 4; melittin	3	C	94
	Api m 6;	7-8	P	Kettner,p.c.
Bombus pennsylvanicus (bumble bee)	Bom p 1; phospholipase	16	P	95
	Bom p 4; protease		P	95
Blattella germanica (German cockroach)	Bla g 1; Bd90k		C	
	Bla g 2; aspartic protease	36	C	96
	Bla g 4; calycin	21	C	97
	Bla g 5; glutathione transf.	22	C	98
	Bla g 6; troponin C	27	C	98
Periplaneta americana (American cockroach)	Per a 1; Cr-PII		C	
	Per a 3; Cr-PI	72-78	C	98A
	Per a 7; tropomyosin	37	C	Y14854
Chironomus thummi thummi (midges)	Chi t 1-9; hemoglobin	16	C	99
	Chi t 1.01; component III	16	C	P02229
	Chi t 1.02; component IV	16	C	P02230
	Chi t 2.0101; component I	16	C	P02221
	Chi t 2.0102; component IA	16	C	P02221
	Chi t 3; component II-beta	16	C	P02222
	Chi t 4; component IIIA	16	C	P02231

	Chi t 5; component VI	16	C	P02224
	Chi t 6.01; component VIIA	16	C	P02226
	Chi t 6.02; component IX	16	C	P02223
	Chi t 7; component VIIB	16	C	P02225
	Chi t 8; component VIII	16	C	P02227
	Chi t 9; component X	16	C	P02228
Dolichovespula maculata				
(white face hornet)	Dol m 1; phospholipase A1	35	C	100
	Dol m 2; hyaluronidase	44	C	101
	Dol m 5; antigen 5	23	C	102,103
Dolichovespula arenaria				
(yellow hornet)	Dol a 5; antigen 5	23	C	104
Polistes annularies				
(wasp)	Pol a 1; phospholipase A1	35	P	105
	Pol a 2; hyaluronidase	44	P	105
	Pol a 5; antigen 5	23	C	104
Polistes dominulus				
(Mediterranean paper wasp)				
	Pol d 1;			DR Hoffman
	Pol d 4; serine protease	32-34	C	DR Hoffman
	Pol d 5;			P81656
Polistes exclamans				
(wasp)	Pol e 1; phospholipase A1	34	P	107
	Pol e 5; antigen 5	23	C	104
Polistes fuscatus				
(wasp)	Pol f 5; antigen 5	23	C	106
Polistes metricus				
(wasp)	Pol m 5; antigen 5	23	P	106
Vespa crabo				
(European hornet)	Vesp c 1; phospholipase	34	P	107
	Vesp c 5.0101; antigen 5	23	C	106
	Vesp c 5.0102; antigen 5	23	C	106
Vespa mandarina				
(giant asian hornet)	Vesp m 1.01;			DR Hoffman
	Vesp m 1.02;			DR Hoffman
	Vesp m 5;			P81657
Vespula flavopilosa				
(yellowjacket)	Ves f 5; antigen 5	23	C	106
Vespula germanica				
(yellowjacket)	Ves g 5; antigen 5	23	C	106
Vespula maculifrons				
(yellowjacket)	Ves m 1; phospholipase A1	33.5	C	108
	Ves m 2; hyaluronidase	44	P	109
	Ves m 5; antigen 5	23	C	104

Vespula pennsylvanica (yellowjacket)	Ves p 5; antigen 5	23	C	106
Vespula squamosa (yellowjacket)	Ves s 5; antigen 5	23	C	106
Vespula vidua (wasp)	Ves vi 5;	23	C	106
Vespula vulgaris (yellowjacket)	Ves v 1; phopholipase A1	35	C	105A
	Ves v 2; hyaluronidase	44	P	105A
	Ves v 5; antigen 5	23	C	104
Myrmecia pilosula (Australian jumper ant)	Myr p 1;		C	X70256
	Myr p 2;		C	S81785
Solenopsis geminata (tropical fire ant)	Sol g 2;			DR Hoffman
	Sol g 4;			DR Hoffman
Solenopsis invicta (fire ant)	Sol i 2;	13	C	110,111
	Sol i 3;	24	C	110
	Sol i 4;	13	C	110
Solenopsis saevissima (brazilian fire ant)	Sol s 2;			DR Hoffman
H. Foods				
Gadus callarias (cod)	Gad c 1; allergen M	12	C	112,113
Salmo salar (Atlantic salmon)	Sal s 1; parvalbumin	12	C	X97824 X97825
Bos domesticus (domestic cattle) (milk) (see also animals)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77
	Bos d 8; caseins	20-30		77
Gallus domesticus (chicken)	Gal d 1; ovomucoid	28	C	114,115
	Gal d 2; ovalbumin	44	C	114,115
	Gal d 3; conalbumin (Ag22)	78	C	114,115
	Gal d 4; lysozyme	14	C	114,115
	Gal d 5; serum albumin	69	C	X60688
Metapenaeus ensis (shrimp)	Met e 1; tropomyosin		C	U08008
Penaeus aztecus (shrimp)	Pen a 1; tropomyosin	36	P	116

Penaeus indicus (shrimp)	Pen i 1; tropomyosin	34	C	117
Todarodes pacificus (squid)	Tod p 1; tropomyosin	38	P	117A
Haliotis Midae (abalone)	Hal m 1	49	-	117B
Apium graveolens (celery)	Api g 1; Bet v 1 homologue	16*	C	Z48967
	Api g 4; profilin			AF129423
	Api g 5;	55/58	P	P81943
Brassica juncea (oriental mustard)	Bra j 1; 2S albumin	14	C	118
Brassica rapa (turnip)	Bra r 2; prohevein-like protein	25	?	P81729
Hordeum vulgare (barley)	Hor v 15; BMAI-1	15	C	119
Zea mays (maize, corn)	Zea m 14; lipid transfer prot.	9	P	P19656
Oryza sativa (rice)	Ory s 1;		C	U31771
Corylus avellana (hazelnut)	Cor a 1.0401; Bet v 1 homologue	17	C	AF136945
Malus domestica (apple)	Mal d 1; Bet v 1 homologue		C	X83672
	Mal d 2; thaumatin homologue		C	AJ243427
	Mal d 3; lipid transfer protein	9	C	Pastorello
Pyrus communis (pear)	Pyr c 1; Bet v 1 homologue	18	C	AF05730
	Pyr c 4; profilin	14	C	AF129424
	Pyr c 5; isoflavone reductase homologue	33.5	C	AF071477
Persea americana (avocado)	Pers a 1; endochitinase	32	C	Z78202
Prunus armeniaca (apricot)	Pru ar 1; Bet v 1 homologue		C	U93165
	Pru ar 3; lipid transfer protein	9	P	
Prunus avium (sweet cherry)	Pru av 1; Bet v 1 homologue		C	U66076
	Pru av 2; thaumatin homologue		C	U32440
	Pru av 4; profilin	15	C	AF129425
Prunus persica (peach)	Pru p 3;lipid transfer protein	10	P	P81402

Sinapis alba (yellow mustard)	Sin a 1; 2S albumin	14	C	120
Glycine max (soybean)	Gly m 1.0101; HPS	7.5	P	121
	Gly m 1.0102; HPS	7	P	121
	Gly m 2	8	P	A57106
	Gly m 3; profilin	14	C	AJ223982
Arachis hypogaea (Peanut)	Ara h 1; vicilin	63.5	C	L34402
	Ara h 2; conglutin	17	C	L77197
	Ara h 3; glycinin	60	C	AF093541
	Ara h 4; glycinin	37	C	AF086821
	Ara h 5; profilin	15	C	AF059616
	Ara h 6; conglutin homolog	15	C	AF092846
	Ara h 7; conglutin homolog	15	C	AF091737
Actinidia chinensis (kiwi)	Act c 1; cysteine protease	30	P	P00785
Solanum tuberosum (potato)	Sola t 1; patatin	43	P	P15476
Bertholletia excelsa (Brazil nut)	Ber e 1; 2S albumin	9	C	P04403,M17146
Juglans regia (English walnut)	Jug r 1; 2S albumin		C	U66866
	Jug r 2; vicilin	44	C	AF066055
Ricinus communis (Castor bean)	Ric c 1; 2S albumin		C	P01089

I. Others

Anisakis simplex (nematode)	Ani s 1;	24	P	A59069
	Ani s 2; paramyosin	97	C	AF173004
Ascaris suum (worm)	Asc s 1;	10	P	122
Den n (red coral)	Den n 1;			Onizuka, p.c.
Hevea brasiliensis (rubber)	Hev b 1; elongation factor	58	P	123,124
	Hev b 2; (1,3-glucanase	34/36	C	125
	Hev b 3	24	P	126,127
	Hev b 4; component of microhelix protein complex	100/110/115	P	128
	Hev b 5	16	C	U42640
	Hev b 6.01 hevein precursor	20	C	M36986/p02877
	Hev b 6.02 hevein	5	C	M36986/p02877

	Hev b 6.03 C-terminal fragment	14	C	M36986/p02877
	Hev b 7; patatin homologue	46	C	U80598
	Hev b 8; profilin	14	C	Y15042
	Hev b 9; enolase	51	C	AJ132580/ AJ132581
	Hev b 10; Mn-superoxide dismut.	26	C	AJ249148
Ctenocephalides felis felis (cat flea)	Cte f 1;			
	Cte f 2; M1b	27	C	AF231352
Homo sapiens (human autoallergens)	Hom s 1;	73*	C	Y14314
	Hom s 2;	10.3*	C	X80909
	Hom s 3;	20.1*	C	X89985
	Hom s 4;	36*	C	Y17711
	Hom s 5;	42.6*	C	P02538

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MW Sequence Accesion # or
Allergen source Systematic and original names
kDa data References

2000.03.01 Jørgen Nedergaard Larsen and Henning Løwenstein, ALK-Abelló, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark
ftp://biobase.dk/pub/who-iuis/allergen.list

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